REMARKS

Claims 57-67 are pending in the present application. Applicants acknowledge that the drawings in this application are objected to by the Draftsperson under 37 C.F.R. § 1.84. As indicated in the Office Action, these drawings can be provided upon allowance of the application. Therefore, applicants will provide formal drawings upon allowance of the application. In light of the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Objection to the Specification

The Office Action states that the disclosure is objected to because the first page of the specification is not numbered.

The specification is amended herein such that the first page of the specification is now numbered. Applicants believe this objection has been overcome and respectfully request its withdrawal.

II. Oath/Declaration

The Office Action states that a new oath or declaration is required because non-initialed and/or non-dated alterations have allegedly been made to the oath or declaration. Furthermore, the Office Action states that applicant has not given a post office address anywhere in the application papers as required by 37 C. F.R. § 1.33(a), which was in effect at the time of filing of the oath or declaration and the specification to which the oath or declaration is directed has allegedly not been adequately identified.

Applicants will provide a new declaration in compliance with 37 C.F.R. 167(a) identifying this application by application number and filing date. Applicants believe this new Declaration will overcome the objection raised by the Examiner and respectfully request its withdrawal. The new declaration is not filed herewith, due to difficulties in obtaining a signature of one of the inventors who now resides in China, but will be submitted as soon as possible.

III. Rejection Under 35 U.S.C. § 102(a)

Claims 57-67 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ren et al. (Protein Science (1996), Vol. 5, pages 1833-1843).

Applicants note that the present application was filed on April 11, 1997, which is less than one year before the September publication date of Ren *et al.* and that the cited reference is the inventors' own publication. This reference lists co-authors not listed as co-inventors and is properly cited. Applicants include herewith a Katz-type Declaration, as Exhibit A which describes the contribution to the research of each of the non-inventor co-authors listed on the paper.

Specifically, the Declaration by co-author and co-inventor Dr. Alasdair C. Steven states that neither Dr. George K. Lewis nor Ms. Emily G. Locke contributed to the conception of the claimed invention, but, rather made other contributions to the work described in Ren et al. Therefore, Dr. Lewis and Ms. Locke are not co-inventors as to the presently claimed invention. Thus, the Ren et al. reference does not disclose the claimed invention "by others" and therefore should be removed as a 35 U.S.C. § 102(a) reference. On this basis, applicants believe the present rejection has been overcome and its withdrawal is respectfully requested.

IV. Rejections Under 35 U.S.C. § 103(a)

A. According to the Office Action, claims 57, 62, 63, 64, 66 and 67 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ladner et al. (U.S. Patent No. 5,403,484) in view of MacDonald et al. (EMBO Journal, Vol. 3: No. 12, pages 2863-2871 (1984)). The Office Action states that Ladner et al. show that viruses expressing chimeric binding proteins can be useful in producing novel enzymes and hormones. Novel binding proteins against a molecule of interest encoding a protein comprising a binding domain are utilized to display a protein on the outer surface of a chosen bacterial cell, spore, or phage. The protein may be expressed as an insert in a chimerical bacterial outer surface protein (OSP). Ladner et al. state that "[a]ll bacteria exhibit proteins on their outer surface." (Column 60, lines 58-61). Further stated in Ladner is that to obtain appropriate display it may be necessary to add one or more linker amino acids between the OSP and the potential binding domain (PBD). (Column 71, lines 13-22). According to the Office Action, Ladner et al. differ from the instant invention in not specifically employing a T4 phage in the chimeric composition.

Further stated in the Office Action is that MacDonald et al. disclose DNA sequence and transcriptional patterns in T4 phage. The T4 phage is taught to be a suitable lattice protein in the instant invention. Also stated in the Office Action is that in an area between 15 and 18 kb on the standard phage T4 map, the novel gene 69 is localized. This 69 gene (molecule of interest) codes for two overlapping proteins that share a common C-terminal segment. The two proteins are expressed from different transcripts that are under different regulation. The smaller protein, gp69, can be expressed from Escherichia coli-like promoter, but the expression of the larger protein, gp69 is delayed. The gene (69) is bracketed by DNA adenine methylase (linker) and the late gene SOC (T4 dispensable polypeptide).

According to the Office Action, it would have been obvious to one of ordinary skill in the

art at the time the invention was made to use the T4 phage surface lattice protein as taught by MacDonald et al. in a chimera composition as disclosed by Ladner et al. to produce outer capsid molecule display, because such T4 phage molecules as taught by MacDonald et al. are well known in the art. Further stated in the Office Action is that a person of ordinary skill in the art would have had a reasonable expectation of success utilizing T4 phage given the knowledge on its detailed structure.

Applicants respectfully point out to the Examiner that the Ladner et al. reference describes a method of phage display in which a molecule of interest is displayed directly on the surface of the phage. The molecule of interest is fused with an OSP, defined as an outer surface protein, e.g. coat protein of a phage or LamB from *E.coli*, which must pass through the secretion system of the phage in order to be displayed on the surface. An outer surface protein, as defined by Ladner et al., is not a dispensable polypeptide. Therefore, Ladner et al. does not teach or suggest linking a molecule of interest to a dispensable polypeptide that then binds a surface lattice protein. In fact, Ladner et al. do not even mention a dispensable polypeptide of a phage. Although Ladner et al. state that to obtain appropriate display it may be necessary to add one or more linker amino acids between the OSP and the potential binding domain (PBD), this clearly describes a linkage between the molecule of interest and an OSP. In the system described in Ladner et al., the OSP is the equivalent of the surface lattice protein of the presently claimed system. Thus, the linkage described in Ladner et al. cannot be equivalent to linking a molecule of interest to a T4 dispensable polypeptide that then binds a surface lattice protein. Ladner et al. suggests no linkage that would create a chimera equivalent to the chimera in the presently claimed composition. Ladner et al. also gives no motivation to take the very different approach of the present invention for displaying a polypeptide.

Applicants reiterate that, if anything, the teachings of Ladner et al. would motivate one of skill in the art to fuse a molecule of interest with a coat protein, not with a dispensable

polypeptide that would then bind to the surface lattice protein. Furthermore, one skilled in the art would not be motivated to combine the teachings of this reference with the teachings of MacDonald et al. because MacDonald et al. merely discloses the genetic location of three genes on the T4 phage genetic map. One of these genes, SOC (surface outer capsid), is a dispensable polypeptide, but there is no method or motivation stated or suggested for utilizing SOC to make any composition, much less any composition of the present invention. Therefore, there is no teaching or suggestion in MacDonald et al. or Ladner et al., alone or in combination that would allow one of skill in the art to arrive at the claimed invention. Thus, applicants respectfully request withdrawal of this rejection.

B. The Office Action states that claims 58, 59, 60, 61 and 65 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ladner et al. in view of MacDonald et al. and in further view of Aebi et al.

According to the Office Action, Ladner et al in view of MacDonald et al. differ from the instant invention in failing to teach the dispensable polypeptide-HOC and the different types of molecules of interest that may be expressed in this system. However, Aebi et al. disclose that the T4 phage as two dispensable capsids, namely soc and hoc. The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the HOC as a dispensable polypeptide and express antigens, enzymes or immunoglobulins as specific molecules of interest as taught by Aebi et al. in the method of Ladner et al. in view of MacDonald et al. to perform outer capsid display, because such dispsenable polypeptides and molecules of interest as taught by Aebi et al. are well known in the art . The Office Action further states that a person of ordinary skill in the art would have had a reasonable expectation of success utilizing such materials, because they were already shown to be operable in the prior art. One having ordinary skill in the art would have been motivated to do this because Aebi et al. taught that compositions comprising soc and hoc lattices are much more stable. The Office

Action also states that one would be motivated to link molecules of interest to the dispensable polypeptides in order to increase stability of the construct against dissociation and elevated temperatures while preserving phage display capacity (Aebi et al., page 697, second paragraph).

As stated above, the Ladner et al. reference describes a method of phage display in which a molecule of interest if displayed directly on the surface of the phage. The molecule of interest is fused with an OSP, defined as an outer surface protein, e.g. coat protein of a phage or LamB from *E.coli*, which must pass through the secretion system of the phage in order to be displayed on the surface. An outer surface protein, as defined by Ladner et al., is not a dispensable polypeptide. Therefore, Ladner et al. does not teach or suggest linking a molecule of interest to a dispensable polypeptide that then binds a surface lattice protein. Although Ladner et al. state that to obtain appropriate display it may be necessary to add one or more linker amino acids between the OSP and the potential binding domain (PBD), this is a linkage between the molecule of interest and an OSP. This linkage is not equivalent to linking a molecule of interest to a T4 dispensable polypeptide that then binds a surface lattice protein.

Applicants reiterate that, if anything, the teachings of Ladner et al. would motivate one of skill in the art to fuse a molecule of interest with a coat protein, not with a dispensable polypeptide that would then bind to the surface lattice protein. Furthermore, one skilled in the art would not be motivated to combine the teachings of this reference with the teachings of MacDonald et al. because MacDonald et al. merely discloses the genetic location of three genes on the T4 phage genetic map. One of these genes, SOC (surface outer capsid), is a dispensable polypeptide, but there is no method disclosed for utilizing SOC to make any composition, much less any composition of the present invention.

Also, one of skill in the art would not be motivated to combine the teachings of Ladner et al. and MacDonald et al. with the teaching of Aebi et al. because even with the knowledge of the

existence of dispensable capsids, there is no suggestion in Aebi et al. that these dispensable polypeptides can be linked to molecules of interest to make a chimera that would then bind to a surface lattice protein. Although Aebi et al. state that soc and hoc-containing lattices are more stable to dissociation in sodium dodecyl sulfate at elevated temperatures than the P23 lattices alone, there is no teaching or suggestion in Aebi et al. that these dispensable polypeptides can be linked to molecules of interest to make a chimera that would still bind to a surface lattice protein and not disrupt stability. Furthermore, there is no suggestion in Aebi et al. that soc or hoc would be useful for linking to a molecule of interest for the purpose of displaying the molecule of interest. Therefore, prior to applicant's invention, there was no reasonable expectation that a dispensable polypeptide can be linked to a molecule of interest and still retain the ability to bind intact phage. Thus, there is no teaching or suggestion in Ladner et al., MacDonald et al. or Aebi et al., alone or in combination that would allow one of skill in the art to arrive at the claimed invention. Therefore, applicants believe this rejection has been overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Payment in the amount of $1,240.00 ($920.00 for a three month extension of time and $320.00 for a Notice of Appeal) is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled Credit Card Payment Form PTO-2038. Also included herewith, is a Notice of Appeal and a Request for Extension of Time. This amount is believed to

be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

Gwendolyn D. Spratt
Registration No. 36,016

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX AF, Commissioner of Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — Date: 1-02-02

PHAGE DISPLAY OF INTACT DOMAINS AT HIGH COPY NUMBER

The work described herein was carried out, in part, at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health. The government therefore may have certain rights in the invention.

Background of the Invention

The field of the invention is phage display.

Filamentous phage-based display systems (as described, for example, in Smith, *Science* 228:1315-1317, 1985) have found widespread use in molecular biology, including many immunologic applications such as antigen presentation and the immuno-isolation of desired recombinants by "biopanning" (Marks et al., *J. Biol. Chem.* 267:16007-16010, 1992; Smith et al., *Gene* 128:37-42, 1993; Williamson et al., *Proc. Natl. Acad. Sci. USA,* 90:4141-4145, 1993). However, with filamentous phages, peptides that may be displayed from the major coat protein are limited in size to 6-10 amino acid residues (Kishchenko et al., *J. Mol. Biol.* 241:208-213, 1994; Iannolo et al., *J. Mol. Biol.* 248:835-844, 1995), although somewhat longer peptides can be displayed by co-assembly with the wild-type coat protein (Perhan et al., *FEMS Microbiol. Rev.* 17:25-31, 1995). Full-length polypeptides can be displayed on minor phage proteins, but only at very low copy number (Parmley and Smith, *Gene* 73:305-318, 1988). Moreover, the requirement that the fusion protein should pass through the secretion system of *Escherichia coli* may pose problems of toxicity for the host, or for correct folding of the displayed protein (Skerra and Plückthun, *Protein Eng.* 4:971-979, 1991).

Summary of the Invention

Described herein is a phage display system in which the molecules to be displayed (i.e., molecules of interest) are bound to dispensable capsid polypeptides such as SOC (small outer capsid) and HOC (highly antigenic outer capsid)

A-

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Steven et al.	)	
	)	Group Art Unit: 1641
Serial No. 08/837,301	)	
	)	
	)	Examiner: Cook, L.
Filed: April 11, 1997	)	
	)	
	)	
For: "PHAGE DISPLAY OF INTACT DOMAIN AT HIGH COPY NUMBERS"	)	

DECLARATION OF ALASDAIR C. STEVEN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

NEEDLE & ROSENBERG, P.C.
Suite 1200
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127 Peachtree Street, N.E.
Atlanta, Georgia 30303-1811

Dear Sir:

I, Alasdair Steven, a citizen of the United States, residing at 2832 Blue Spruce Lane, Silver Springs, Maryland 20906, declare that:

1. I am a co-inventor with Paul Wingfield, Lindsay Black, and Zhaojun Ren of the above-referenced patent application and of the subject matter described and claimed therein.

2. I am co-author of the article by Zhaojun Ren, G.K. Lewis, Paul Wingfield, E.G. Locke, Alasdair C. Steven and Lindsey Black entitled "Phage display of intact domains at high

copy number: A system based on SOC, the small outer capsid protein of bacteriophage T4 " *Protein Science* 5:1833-1843, September 1996.

3. During the period of time in which the research described in the Ren *et al.* reference was conducted, Dr. George K. Lewis provided a reagent, the V3 clone, used in the experiments described in the Ren et al. reference. Dr. Lewis had no role in the conception of the claimed invention. Therefore, he was included as a co-author in the Ren et al. reference for this contribution, but was not involved in the conception of the claimed invention.

4. During the period of time in which the research described in the Ren et al. reference was conducted, Emily G. Locke was a technician in my lab and performed experiments at my direction and under my supervision. Emily G. Locke had no role in the conception of the claimed invention. Therefore, she was included as a co-author in the Ren et al. reference for this contribution, but was not involved in the conception of the claimed invention.

6. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or document or any patent issuing therefrom.

12/28/01
Date

Alasdair C. Steven
ALASDAIR C. STEVEN